

Supplement

Botulinum Neurotoxin-A Injected Intrastriatally into Hemiparkinsonian Rats Improves the Initiation Time for Left and Right Forelimbs in Both Forehand and Backhand Directions

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1. Supplement

Table 1. List of publications of stepping test evaluating adjusting steps of the forepaws and measuring the "classical" initiation time according to Olsson et al. (1995) in hemi-parkinsonian rats after 6-OHDA lesion. Abbreviations: b – backhand, contra – contralateral, f – forehand, ipsi – ipsilateral, not done – experiment not done, not shown – experiment done, but result not conveyed, S-D - Sprague-Dawley rat, W – Wistar rat.

Publication	Strain, gender	Site of 6-OHDA Dosage of 6-OHDA Pretreatment with desipramine	Adjusting steps, initiation time, time after lesion	Adjusting steps (number of steps) mean $\pm$ SEM or SD	Initiation time in seconds (s) mean $\pm$ SEM or SD
Antala et al. 2012 [1]	W, m	- Right striatum or right SN - 7 μ g 6-OHDA - not done	3 weeks	6-OHDA: contra (f) 4.50 ± 0.56 , (b) 5.33 ± 0.87 ; ipsi not shown Sham: contra (f) 10.67 ± 0.88 , (b) 11.83 ± 1.19 ; ipsi not shown	6-OHDA: contra 17.17 ± 1.8 ; ipsi not shown Sham: contra 4 ± 0.58 ; ipsi not shown

Badstuebner et al. 2017 [2]	W, m	- Right MFB - 24 µg 6-OHDA - not done	12-14 days	6-OHDA: contra stepping bias (%) (f) approx. 10%, (b) approx. 29%; ipsi not shown Sham: contra stepping bias % (f) approx. 50%, (b) approx. 51%; ipsi not shown	6-OHDA: contra approx. 8; ipsi approx. 3 Sham: contra approx. 1,5; ipsi approx. 1
Fang et al. 2006a [3]	S-D, m	- Lateral sector of the striatum (one or four lesions) - 7 µg 6-OHDA - not done	3 weeks	6-OHDA: contra (f) approx. 1.7, (b) approx. 8; ipsi not shown Sham: not done	6-OHDA: contra approx. 25 (one lesion), approx. 30 (four lesion); ipsi not shown Sham: not done
Fang et al. 2006b [4]	S-D, m	- Right striatum (one to four lesions) - 7 µg 6-OHDA - not done	3 weeks	6-OHDA: contra (f) approx. 1.8 (one lesion), (f) approx. 1.9 (four lesion), (b) approx. 5.8 (one lesion), (b) approx. 5.9 (four lesion); ipsi (f) approx. 7 (one lesion), (f) approx. 7.2 (four lesion), (b) approx. 11,8 (one lesion), (b) approx. 11 (four lesion) Sham: not shown	6-OHDA: contra approx. 19 (one lesion-four lesion); ipsi approx. 3 Sham: not shown
Fang et al. 2010 [5]	S-D, m	- Lateral sector of the striatum (one or four lesions) - 7 µg 6-OHDA - not done	3 weeks	6-OHDA: contra (f) approx. 1 (one lesion), (f) approx. 1 (four lesion), (b) approx. 8 (one lesion), (b) approx. 7.5 (four lesion); ipsi not shown Sham: not done	6-OHDA: contra approx. 28 (one lesion), approx. 34 (four lesion); ipsi not shown Sham: not done
Mukhida et al. 2001 [6]	W, f	- Right ascending mesostriatal dopaminergic pathway - 3.6 µg 6-OHDA - not done	3 weeks	6-OHDA: contra (f) approx. 3; ipsi (f) approx. 28 Sham: not done	6-OHDA: contra approx. 20; ipsi approx. 2 Sham: not done

Olsson et al. 1995 [7]	S-D, f	- Right ascending mesostriatal dopamine pathway - 3.6 µg 6-OHDA - not done	3-5 weeks	6-OHDA: contra (f) approx.2, (b) approx. 1-2; ipsi (f) approx. 12, (b) approx. 12 Sham: not done	6-OHDA: contra approx. 60-120; ipsi approx.1-2 Sham: not done
Pinna et al. 2007 [8]	S-D, m	- Left MFB - 8 µg 6-OHDA - 10 mg/kg	2-3 weeks	6-OHDA: contra (f) approx. 2 (2W) and 1 (3W) weeks after lesion, (b) approx. 3 (2W) and 4 (3W) after lesion; ipsi (f) approx. 7 (2W) and 6 (3W) weeks after lesion (b) approx. 9 (2W) and 8 (3W) weeks after lesion Sham: not done	6-OHDA: contra approx. 5 (2 W) and 10 (3W) weeks after lesion; ipsi approx. 1 (2 W and 3W) weeks after lesion Sham: not done
Pinna et al. 2010 [9]	S-D, m	- Left MFB - 8 µg 6-OHDA - 10 mg/kg	4 weeks	6-OHDA: contra (f) approx. 2 (2W) and 1 (3W) weeks after lesion, (b) approx. 3 (2W) and 4 (3W) weeks after lesion; ipsi not shown Sham: not done	6-OHDA: contra approx. 7 (2W) 15 (3W) weeks after lesion; ipsi not shown Sham: not done
Singh et al. 2006a [10]	S-D, f	- Lateral striatum - 8 µg 6-OHDA - not done	5 weeks	6-OHDA: contra (f) 6 ± 1, (b) 7 ± 2; ipsi not shown Sham: not done	6-OHDA: contra 16 ± 2; ipsi not shown Sham: not done
Singh et al. 2006b [11]	S-D, f+m	- Striatum - 8 µg 6-OHDA - not done	4-5 weeks	6-OHDA: contra (f) 4 ± 1, (b) 5 ± 2; ipsi not shown Sham: contra (f) 12 ± 1, (b) 13 ± 2; ipsi not shown	6-OHDA: contra 15 ± 1; ipsi not shown Sham: contra 2 ± 1; ipsi not shown
Sun et al. 2010 [12]	S-D, m	- Striatum (one or four lesions) or MFB - 7 µg 6-OHDA - not done	3 weeks	6-OHDA: contra (for one, four, MFB lesions) (f) approx. 2, (b) approx. 4; ipsi (for one, four, MFB lesions) (f) approx. 6-7, (b) approx. 11-12 Sham: not shown	6-OHDA: contra (for one, four, MFB lesions) approx. 20; ipsi (for one, four, MFB lesions) approx. 5 Sham: not shown

Sun et al. 2013 [13]	S-D, m	- Striatum (one or four lesion) or MFB - 7 µg 6-OHDA - not done	1 and 6 months	6-OHDA: contra (for one, four, MFB lesions) (f) approx. 2, (b) approx. 4; ipsi (for one, four, MFB lesions) (f) approx. 6, (b) approx. 12 Sham: not shown	6-OHDA: contra (for one, four, MFB lesions) approx. 20; ipsi approx. 5 Sham: not shown
Zhang et al. 2016 [14]	S-D, m	- MFB - 6 µl 6-OHDA - not done	4 weeks	not done	6-OHDA: contra approx. 80; ipsi not shown Sham: contra approx. 1; ipsi not shown
Present publication (newly defined initiation time)	W, m	- right MFB - 24 µg 6-OHDA - not done	4 weeks	6-OHDA: contra (f) 3.958 ± 0.136 , (b) 6.813 ± 0.136 ; ipsi (f) 10.993 ± 0.160 , (b) 12.153 ± 0.175 Sham: not done	6-OHDA: contra (f) 3.629 ± 0.110 , (b) 3.493 ± 0.087 ; ipsi (f) 0.622 ± 0.018 , (b) 0.536 ± 0.019 Sham: not done

Table 2. List of publications evaluating adjusting steps of the forepaws in hemi-parkinsonian rats after 6-OHDA lesion. Abbreviations: b – backhand, contra – contralateral, f – forehand, ipsi – ipsilateral, not done – experiment not done, not shown – experiment done, but result not conveyed, S-D - Sprague-Dawley rat, W – Wistar rat.

Publication	Strain, gender	Site of 6-OHDA Dosage of 6-OHDA Pretreatment with desipramine	Adjusting steps, time after lesion	Adjusting steps, number of steps of contralateral and ipsilateral paw mean $\pm$ SEM or SD
Abedi et al. 2013 [15]	S-D, m	- Right GP - 12.5 μ g 6-OHDA - 25 mg/kg	4 weeks	6-OHDA: contra (f) 1.42 ± 0.32 ; ipsi (f) 5.25 ± 0.22 Sham: contra (f) 5.25 ± 0.32 ; ipsi (f) 5.23 ± 0.34
Acuña-Lizama et al. 2013 [16]	W, m	- Right SNpc - 10.5 μ g 6-OHDA - 25 mg/kg	11-12 weeks	6-OHDA: contra (f) 0.5 ± 0.2 (Gr. A, caffeine after lesion) and 13.5 ± 0.3 (Gr. B, theophylline after lesion); ipsi (f) 13.4 ± 0.3 (Gr. A) and 1.9 ± 1.0 (Gr. B) Sham: not done
Antipova et al. 2017 [17]	W, m	- Right MFB - 24 μ g 6-OHDA - not done	4 weeks	6-OHDA: contra (f) 3.95 ± 0.13 , (b) 6.70 ± 0.17 ; ipsi (f) 10.93 ± 0.13 , (b) 12.02 ± 0.13 Sham: contra (f) 3.98 ± 0.19 , (b) 7.04 ± 0.24 ; ipsi (f) 11.13 ± 0.18 , (b) 12.42 ± 0.18
Baker et al. 2000 [18]	W, f	- Right ascending nigrostriatal pathway - 3.6 μ g of 6-OHDA - not done	2 weeks	6-OHDA: contra approx. 4; ipsi approx. 24 (total number in both forehand and backhand directions) Sham: not done
Barneoud et al. 2000 [19]	OFA, f	- Experiment 1 and 2 – striatum Experiment 3 – MFB - 10 und 20 μ g 6-OHDA - not done	1 and 6 weeks	6-OHDA (complete lesion, MFB): contra (f) approx. 4, (b) approx. 11; ipsi (f) approx. 13, (b) approx. 13 Sham: contra (f) approx. 13, (b) approx. 13, ipsi (f) approx. 13, (b) approx. 13

Betts et al. 2011 [20]	S-D, m	- above the SNpc - 12 µg 6-OHDA - 25 mg/kg desipramine and 5 mg/kg pargyline	6 days	6-OHDA: use of contra paw (% of pre-lesion) contra (f) approx. 50%, (b) approx. 40%; ipsi not done Sham: not done
Bordia et al. 2015 [21]	S-D, m	- MFB - 3 µg 6-OHDA - not done	2 to 8 weeks	6-OHDA: number of total steps (100 %) contra (f) approx. 23%; ipsi not done Sham: not done
Cerri et al. 2015 [22]	W, m	- Right striatum - 20 µg 6-OHDA - not done	1 day	6-OHDA: contra (f) approx. 2-3; ipsi not done Sham: contra (f) approx. 10-12; ipsi not done
Chotibut et al. 2017 [23]	S-D, m	- Right MFB - 16 µg 6-OHDA - not done	1, 7 and 17 days	6-OHDA: as group mean lesioned forepaw stepping (%) contra (f) approx. 30 %; ipsi not done Sham: ipsi (f) approx. 100%; contra not done
Dowd et al. 2005 [24]	Lister Hooded, f	- MFB - 12 µg 6-OHDA - not done	2 weeks	6-OHDA : contra (f) approx. 2; ipsi not shown Sham: not done
Dowd and Dunnett 2005 [25]	Lister Hooded, m	- MFB or striatum - MFB - 12 µg 6-OHDA - Striatum - 28 µg 6-OHDA - not done	4 months	6-OHDA: MFB contra (f) approx. 2.5, ipsi not shown Striatum contra (f) approx. 3; ipsi not shown Sham: not done
Frau et al. 2017 [26]	S-D, f + m	- Right MFB - 16 µg 6-OHDA - not done	3 and 4 weeks	6-OHDA: contra (f) approx. 1-5; ipsi (f) approx. 20 Sham: not done
Hahn et al. 2009 [27]	S-D, f	- Right mesostriatal pathway - 10.8 µg 6-OHDA - not done	14 days and 6 weeks	6-OHDA: contra (b) approx. 2-4, ipsi not done Sham: not done

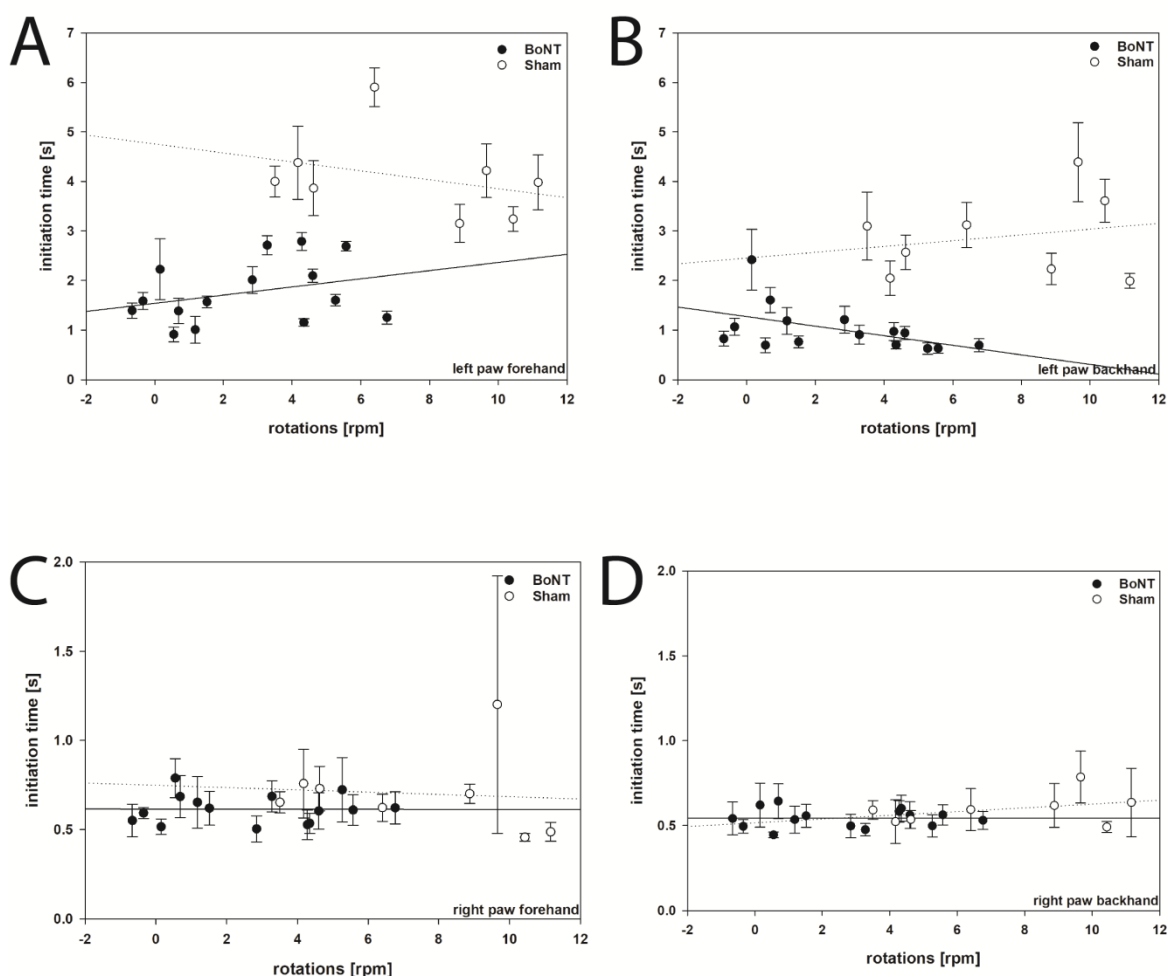
Ivanova et al. 2015 [28]	W, m	- Left MFB - 12 µg 6-OHDA - not done	7, 14, 21 days	Ratio of the numbers of steps made by the impaired forelimb to the total number of steps made by both forelimbs (%). 6-OHDA: contra (f) 20.00 ± 7.45 ; ipsi not done Sham: contra (f) 46.90 ± 3.50 ; ipsi not done
Kim et al. 2011 [29]	S-D, m	- Right MFB - 25 µg 6-OHDA - not done	4 weeks	6-OHDA: contra (f) approx. 2; ipsi (f) approx. 13 Sham: contra (f) approx. 13; ipsi (f) approx. 13
Kirik et al. 1998 [30]	S-D, f	- Right striatum or MFB - Right striatum - 20 µg 6-OHDA - MFB - 13.5 µg 6-OHDA - not done	3 and 8 weeks	6-OHDA: Striatum: contra (f) 6.5 ± 1.1 ; ipsi (f) 10.6 ± 1.1 MFB: contra (f) 1.2 ± 0.4 ; ipsi (f) 9.5 ± 1.6 Sham contra (f) 10.9 ± 0.6 ; ipsi (f) 10.6 ± 0.3
Kirik et al. 2000 [31]	S-D, f	- Right striatum - 20 µg 6-OHDA - not done	4 and 6 weeks	6-OHDA: contra (f) approx. 3-7; ipsi (f) approx. 11-13 Sham: not done
Kirik et al. 2001a [32]	S-D, f	- Right striatum - 28 µg 6-OHDA - not done	4 weeks	6-OHDA: contra (f) approx. 1- 4; ipsi not shown Sham: not done
Kirik et al. 2001b [33]	S-D, f	- Right striatum - 28 µg 6-OHDA - not done	1, 5, 7 and 11 weeks	6-OHDA: contra (f) approx. 2; ipsi not shown Sham: not done
Köllensperger et al. 2007 [34]	W, m	- Left MFB - 8 µg 6-OHDA - not done	4 weeks	6-OHDA: contra (f) 0.72 ± 1.24 , (b) 10.42 ± 1.38 ; ipsi (f) 6.63 ± 4.28 , (b) 12.88 ± 1.68 Sham: contra (f) 9.8 ± 3.80 , (b) 13.67 ± 1.07 ; ipsi (f) 11.2 ± 11.74 , (b) 13.17 ± 0.89

Lettfuss et al. 2012 [35]	S-D, m	- Left MFB - 12 µg 6-OHDA - 20 mg/kg	22 - 24 days	6-OHDA: contra (f) approx. 1-2, (b) approx. 2-2.5; ipsi (f) approx. 13-15, (b) approx. 15-17 Sham: not done
Manfredsson et al. 2007 [36]	S-D, f	- SNpc - 7 µg 6-OHDA - not done	8 and 12 weeks	6-OHDA: contra (f) approx. 2, (b) approx. 9; ipsi (f) approx. 12, (b) approx. 13 Sham: not done
Mendieta et al. 2012 [37]	W, m	- Left striatum - 16 µg 6-OHDA - not done	4 weeks	6-OHDA: contra (f) 4.1 ± 0.4; ipsi (f) 13.5 ± 0.1 Sham: contra (f) approx. 13
Nikkhah et al. 2001 [38]	S-D, f	- Left or right mesostriatal pathway - 7.2 µg 6-OHDA - not done	10 weeks	6-OHDA: contra (f) approx. 1, (b) approx. 5-8; ipsi not shown Sham: not done
Ostock et al. 2014 [39]	S-D, m	- Left MFB - 12 µg 6-OHDA - 25 mg/kg	3-4 weeks	6-OHDA: lesioned forehand steps/intact forehand steps (%) contra (f) approx. 10%, (b) approx. 25%; ipsi not shown Sham: not done
Rosenblad et al. 1998 [40]	S-D, f	- Right striatum - 20 µg 6-OHDA - not done	8 weeks	6-OHDA: contra (f) 6.9 ± 1.0, (b) 10.9 ± 1.1; ipsi (f) 11.2 ± 0.8, (b) 14.1 ± 0.6 Sham: not done
Sampaio et al. 2017 [41]	W, m	- Right striatum - 20 µg 6-OHDA - not done	60 days	6-OHDA: contra (f) approx. 4; ipsi (f) approx. 11 Sham: contra (f) approx. 11, ipsi (f) approx. 11
Sander et al. 2012 [42]	S-D, f	- Left MFB - 8 µg 6-OHDA - not done	3 weeks	6-OHDA: contra (f) approx. 5, ipsi not shown Sham: not done
Seeger-Armbruster and Ameln-Mayerhofer 2013 [43]	S-D, m	- Left MFB - 12 µg 6-OHDA - 20 mg/kg	4 weeks	6-OHDA: contra (f) approx. 3, (b) approx. 4; ipsi (f) approx. 18, (b) approx. 19 Sham: contra (f) approx. 17, (b) approx. 17; ipsi (f) approx. 15, (b) approx. 17
Shin et al. 2014 [44]	S-D, f	- Right MFB - 14 µg 6-OHDA	1 week	Contralateral paw touches rates of ipsilateral paw touches (%) 6-OHDA:

		- not done		contra (b) approx. 20% Sham: not done
Sutton et al. 2013 [45]	S-D, m	- Right MFB - 13.5 µg 6-OHDA - 25 mg/kg desipramine + 50 mg/kg pargyline	3 weeks	6-OHDA : Forelimb contact bias (% ipsilateral/total), (f) approx. 85% Sham: not shown
Tronci et al. 2013 [46]	S-D, f	- MFB - 16 µg - not done	3 weeks	6-OHDA: contra (f+b) approx. 2; ipsi not shown Sham: not done
Tronci et al. 2014 [47]	S-D, m	- Right MFB - 16 µg - not done	3 weeks	6-OHDA: contra (f+b) approx. 2; ipsi not shown Sham: not done
Tronci et al. 2015 [48]	S-D, m	- MFB - 16 µg - not done	3 weeks	6-OHDA: contra (f+b) approx. 2; ipsi not shown Sham: not done
Winkler et al. 1996 [49]	S-D, f	- Right striatum - 20 µg 6-OHDA - not done	4 months	6-OHDA: contra (f) approx. 3, (b) approx. 9; ipsi (f) approx. 11, (b) approx. 13 Sham: not done
Winkler et al. 2002 [50]	S-D, f	- Striatum - 7 µg 6-OHDA - MFB - 10,5 µg 6-OHDA - not done	3 weeks	6-OHDA: (Striatum and MFB) contra (f) approx. 1-2; ipsi (f) approx. 10-12 Sham: not done
Yoon et al. 2014a [51]	W, m	- Right MFB - 8 µg 6-OHDA - not done	1, 4 and 6 weeks after optic fiber implantation	6-OHDA: rate of contra forelimb touches (%) in both forelimb touches contra (b) approx. 15% Sham: not done
Yoon et al. 2014b [52]	W, m	- Right MFB - 8 µg 6-OHDA - not done	2, 4, 8, and 9 weeks	6-OHDA: as contra paw touches rate (%) of the ipsi paw touches contra (b) approx. 10-12% Sham: not done



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3

4 **Figure S1.** Correlation analysis of the initiation time of stepping movements of the left (contralateral)
5 (A,B) and right (ipsilateral) (C,D) forelimbs in right side 6-OHDA-lesioned rats in both forehand
6 (A,C) and backhand (B,D) directions 1 month after the 1. intrastriatal BoNT-A application and
7 apomorphine-induced rotations. Data represent means $\pm$ SEM. Linear regression lines are displayed
8 for BoNT (solid) and Sham (dotted) groups.

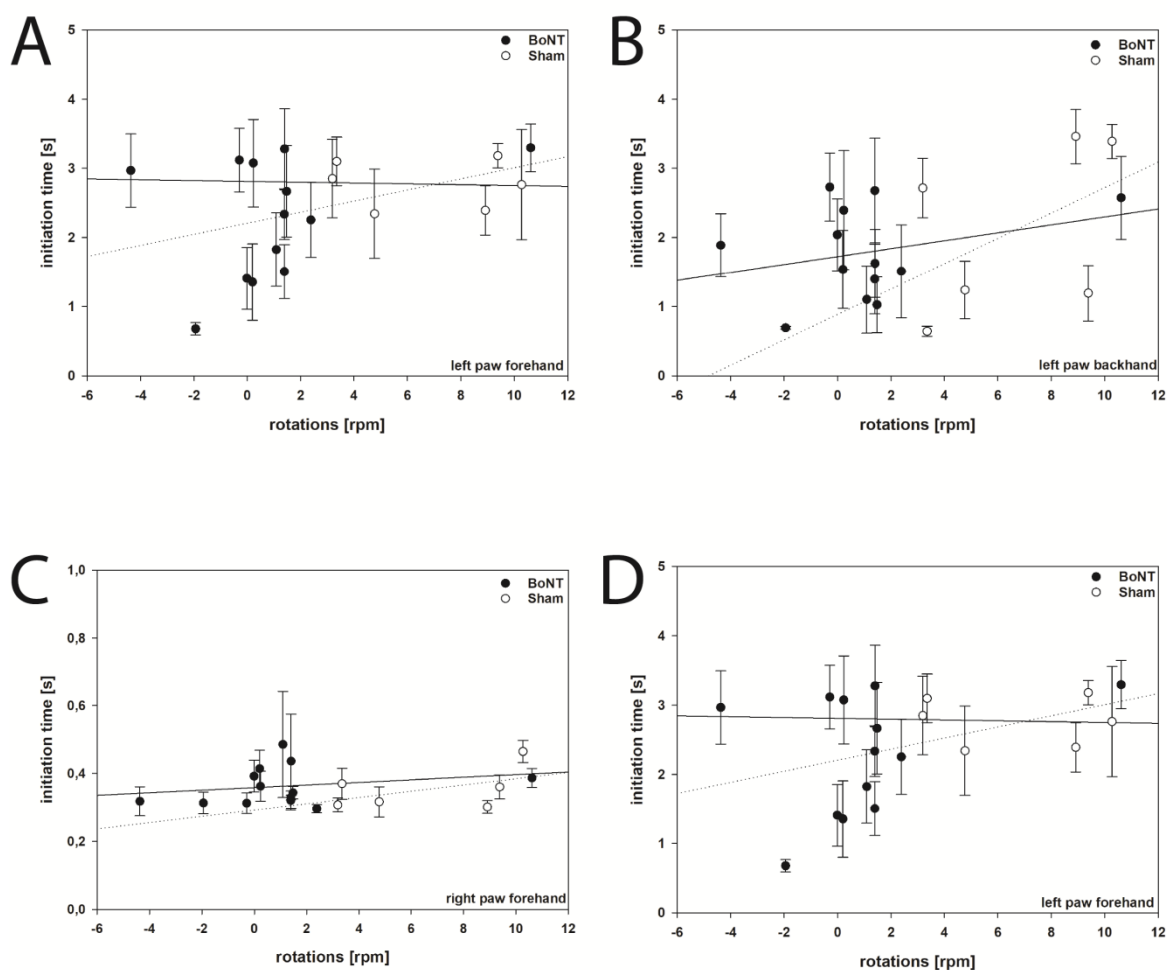


Figure S2. Correlation analysis of the initiation time of stepping movements of the left (contralateral) (A,B) and right (ipsilateral) (C,D) forelimbs in right side 6-OHDA-lesioned rats in both forehand (A,C) and backhand (B,D) directions 1 month after the 2. intrastriatal BoNT-A application and apomorphine-induced rotations. Data represent means $\pm$ SEM. Linear regression lines are displayed for BoNT (solid) and Sham (dotted) groups.

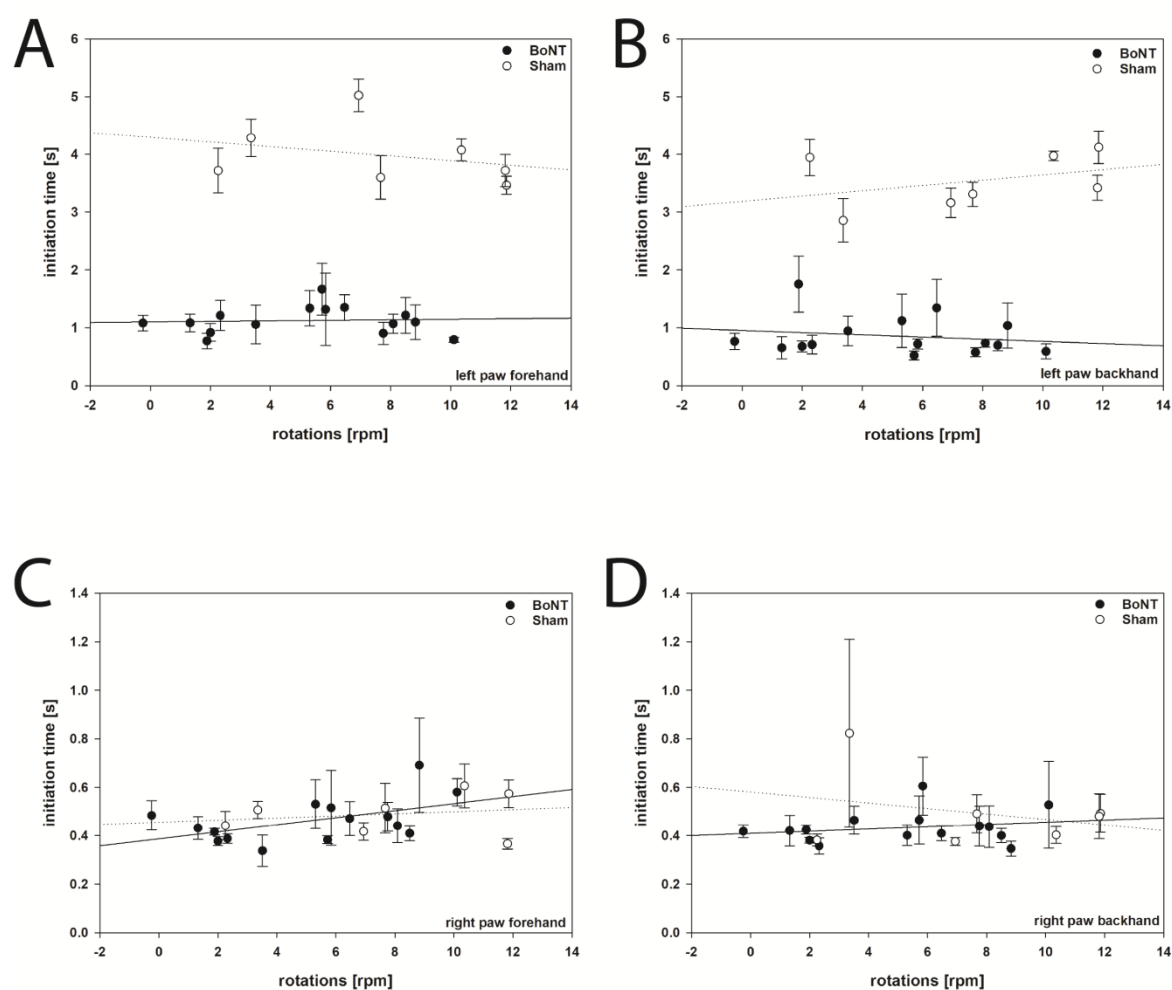


Figure S3. Correlation analysis of the initiation time of stepping movements of the left (contralateral) (A,B) and right (ipsilateral) (C,D) forelimbs in right side 6-OHDA-lesioned rats in both forehand (A,C) and backhand (B,D) directions 3 months after the 1. intrastriatal BoNT-A application and apomorphine-induced rotations. Data represent means $\pm$ SEM. Linear regression lines are displayed for BoNT (solid) and Sham (dotted) groups.

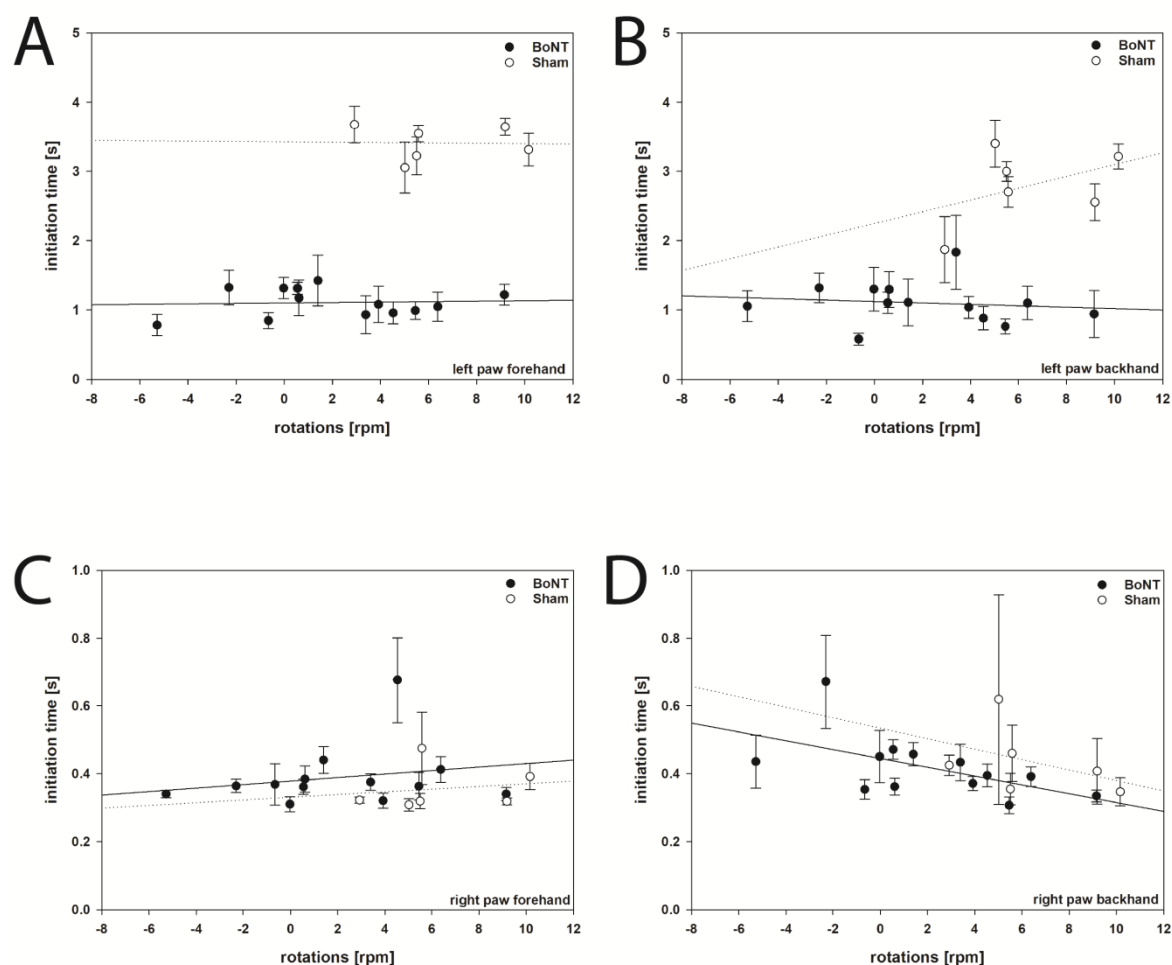


Figure S4. Correlation analysis of the initiation time of stepping movements of the left (contralateral) (A,B) and right (ipsilateral) (C,D) forelimbs in right side 6-OHDA-lesioned rats in both forehand (A,C) and backhand (B,D) directions 3 months after the 2. intrastriatal BoNT-A application and apomorphine-induced rotations. Data represent means $\pm$ SEM. Linear regression lines are displayed for BoNT (solid) and Sham (dotted) groups.

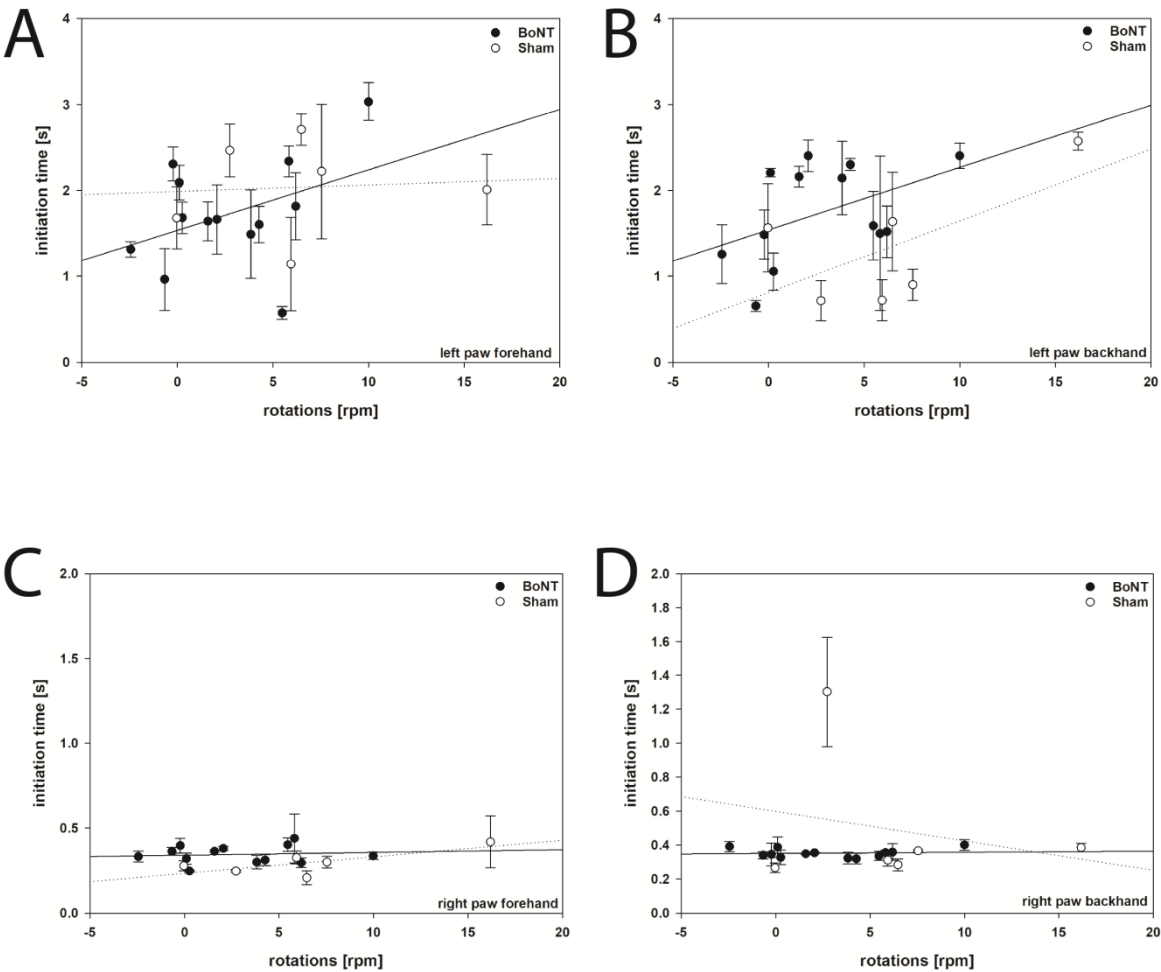


Figure S5. Correlation analysis of the initiation time of stepping movements of the left (contralateral) (A,B) and right (ipsilateral) (C,D) forelimbs in right side 6-OHDA-lesioned rats in both forehand (A,C) and backhand (B,D) directions 6 months after the 1. intrastriatal BoNT-A application and apomorphine-induced rotations. Data represent means $\pm$ SEM. Linear regression lines are displayed for BoNT (solid) and Sham (dotted) groups.

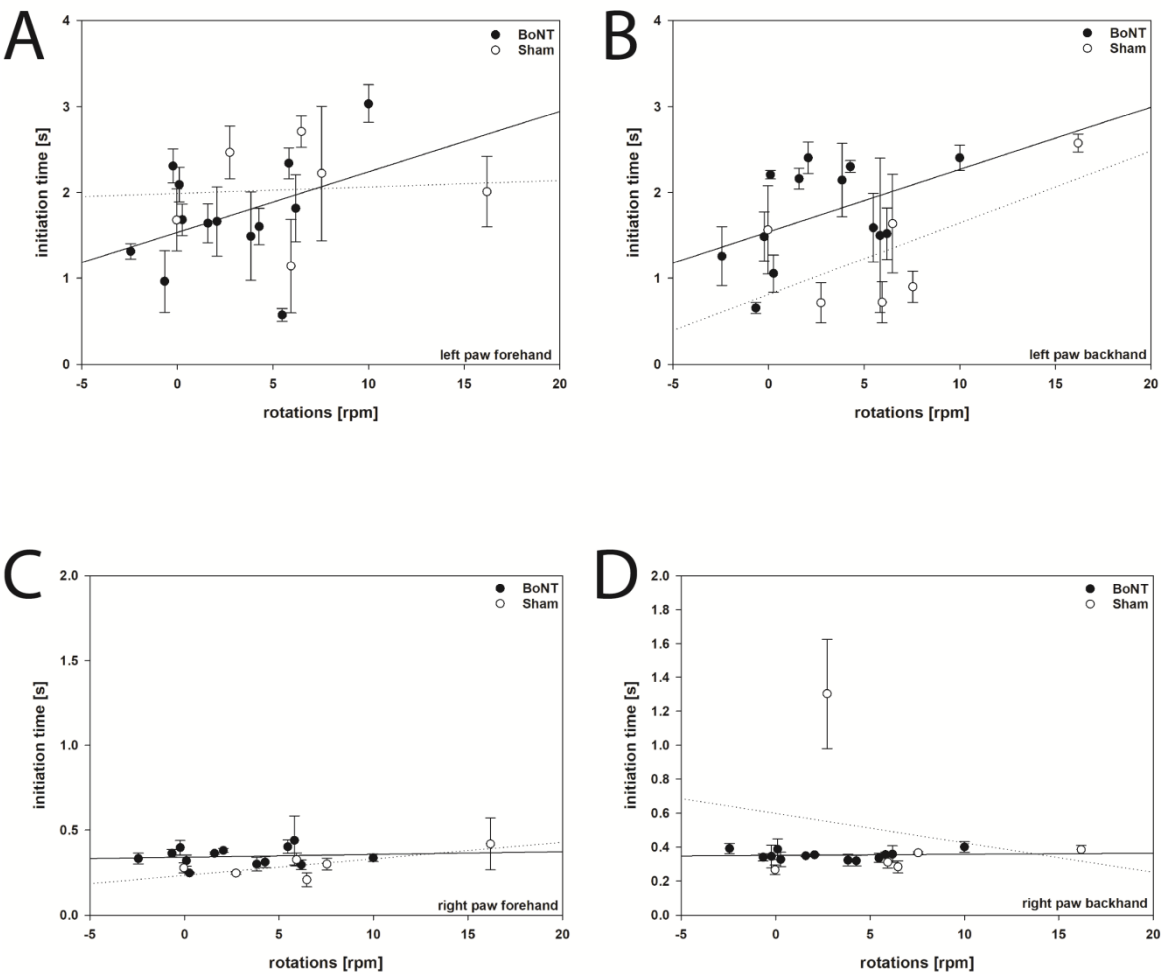


Figure S6. Correlation analysis of the initiation time of stepping movements of the left (contralateral) (A,B) and right (ipsilateral) (C,D) forelimbs in right side 6-OHDA-lesioned rats in both forehand (A,C) and backhand (B,D) directions 6 months after the 2. intrastriatal BoNT-A application and apomorphine-induced rotations. Data represent means $\pm$ SEM. Linear regression lines are displayed for BoNT (solid) and Sham (dotted) groups.

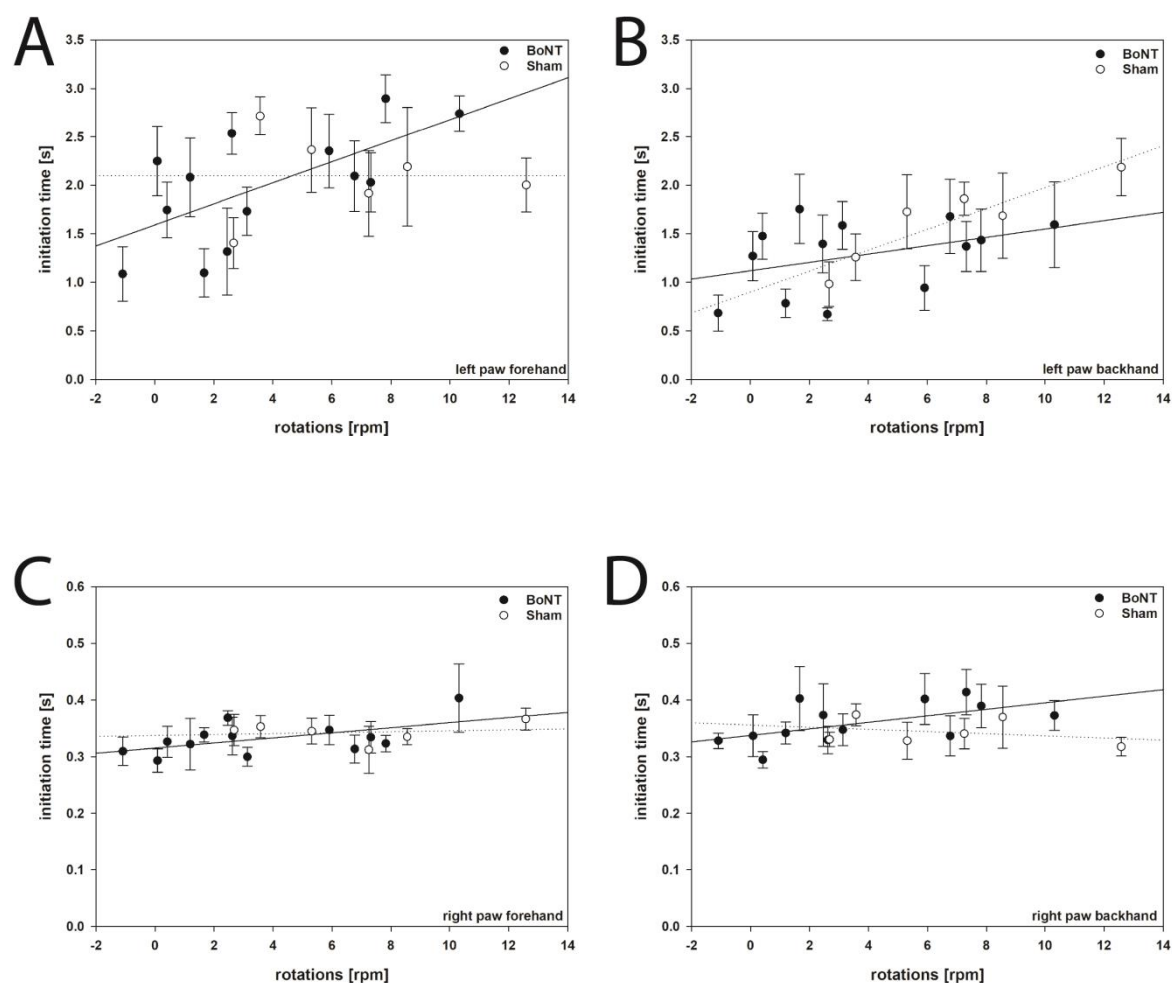


Figure S7. Correlation analysis of the initiation time of stepping movements of the left (contralateral) (A,B) and right (ipsilateral) (C,D) forelimbs in right side 6-OHDA-lesioned rats in both forehand (A,C) and backhand (B,D) directions 9 months after the 2. intrastriatal BoNT-A application and apomorphine-induced rotations. Data represent means $\pm$ SEM. Linear regression lines are displayed for BoNT (solid) and Sham (dotted) groups.

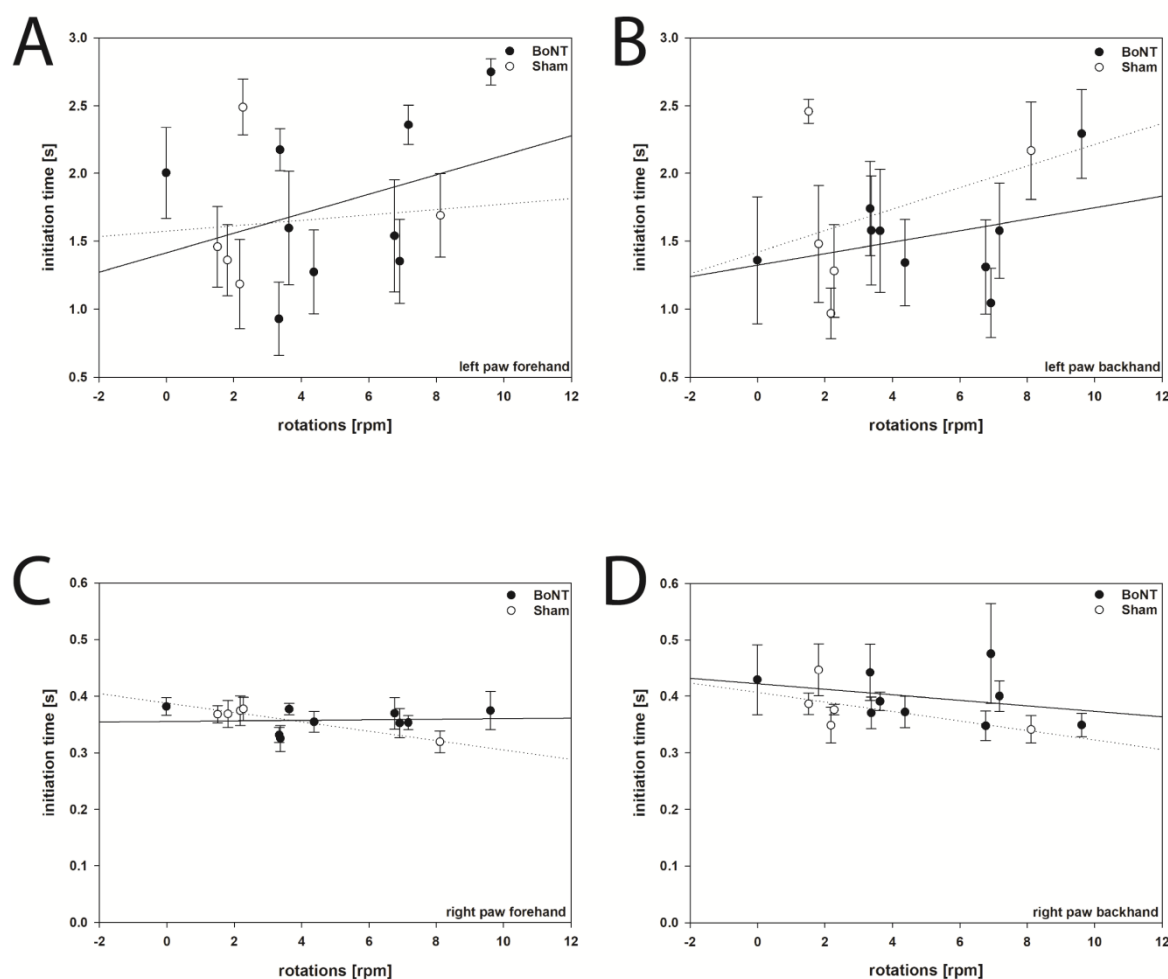


Figure S8. Correlation analysis of the initiation time of stepping movements of the left (contralateral) (A,B) and right (ipsilateral) (C,D) forelimbs in right side 6-OHDA-lesioned rats in both forehand (A,C) and backhand (B,D) directions 12 months after the 2. intrastriatal BoNT-A application and apomorphine-induced rotations. Data represent means $\pm$ SEM. Linear regression lines are displayed for BoNT (solid) and Sham (dotted) groups.

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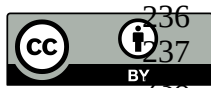
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